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NORFLOXACIN FOR THE PROPHYLAXIS OF TRAVELERS' DIARRHEA IN U.S. MILITARY PERSONNEL

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Abstract. Norfloxacin, an oral fluoroquinolone (dose 400 mg daily), was compared to a placebo in a double blinded randomized trial for the prophylaxis of travelers' diarrhea. The study was of U.S. Navy and Marine Corps personnel on shore leave in Alexandria, Egypt. A total of 222 subjects were available (105 norfloxacin, 117 placebo). In the placebo group, 26% (30/117) developed acute diarrhea vs. 2% (2/105) in the norfloxacin group. There were no significant side effects in either group.

Acute diarrhea is a concern for travelers to developing countries. Although a diarrheal illness rarely produces mortality in healthy populations, it can impair an individual's ability to function. Attack rates vary, but reports of up to 40% are not uncommon.[1] Numerous strategies involving dietary discretion, bismuth subsalicylate prophylaxis and antibiotic prophylaxis have been tried to prevent acute diarrhea.[1–5]

Norfloxacin, the first fluoroquinolone to be approved in the United States, has excellent in vitro activity against most known bacterial enteric pathogens, including *Campylobacter*, *Vibrios*, and *Yersinia*.[6] It is well tolerated, and resistance apparently does not develop as rapidly as with nalidixic acid.[7] Bacterial enteropathogens resistant to other antibiotics are common in Egypt, and may decrease the effectiveness of prophylactic antibiotics.[8,9] The drug was found to be effective at a dose of 200 mg twice daily in Swedish tourists traveling in Africa, Asia, and Latin America.[10] Among students traveling to Mexico, it was 88% effective, and resistant bacteria were not observed.[11]

Although the general use of prophylactic antibiotics by travelers has been discouraged, it may be appropriate in selected populations. This study was undertaken to evaluate the efficacy of norfloxacin in preventing travelers' diarrhea among U.S. Navy and Marine Corps personnel visiting Alexandria, Egypt.

MATERIALS AND METHODS

The study was conducted during August and September 1988 on board the USS *John F. Kennedy*. During the week prior to arrival in Alexandria, Egypt, after completing a 1 week port call to Naples, Italy, volunteers were recruited from the crew of >5,000. Since departing the United States, the carrier had visited no other ports before traveling to Naples and Alexandria.

A brief history was taken from potential study subjects to determine eligibility. Volunteers were disqualified if they gave a history of sensitivity to quinolone antibiotics, renal disease of any type, or diarrhea in the prior month. Informed consent was obtained from each volunteer, and a pre-treatment stool specimen was collected. Subjects were blindly randomized to receive either norfloxacin (400 mg once a day) or an identical appearing placebo.

Study subjects were instructed to take 1 capsule daily beginning the day prior to arrival in Alexandria and to continue until the morning of the ship's departure (7 days). Participants were instructed to report to the medical department immediately if diarrhea developed.

Diarrhea was defined as 4 unformed stools in a 24 hr period, or 3 unformed stools plus any of the following: abdominal pain, cramps, fever, nausea, or vomiting. Diarrhea developing after arrival in port and within 96 hr of leaving Alexandria was attributed to the port call. If a subject developed diarrhea, study prophylaxis was discontinued and the subject was treated as clinically indicated.

Each subject was asked to complete a questionnaire designed to assess compliance, potential side effects, locations visited, and dietary habits while ashore. Questionnaires were completed either when the subject developed diarrhea or 4–5 days after leaving Alexandria.

Pre-treatment stool specimens were stored in

TABLE 1
Comparison of demographic factors between norfloxacin and placebo groups

Factor (mean ± SD)	Placebo (n = 117)	Norfloxacin (n = 105)	*P* value
Age	26.1 ± 6.9	26.5 ± 9.9	0.71
Days ashore	2.8 ± 0.9	2.9 ± 0.9	0.16
Days in Cairo	1.3 ± 0.7	1.4 ± 0.6	0.62
Days in Alexandria	1.4 ± 1.1	1.6 ± 1.2	0.35
No. completing study/No. enrolled	117/138	105/124	0.99
History of previous travel to Egypt	13/116	5/104	0.14
Positive pre-treatment culture	3/69	4/60	0.85

Cary-Blair transport media and cultured at the Naval Medical Research Unit No. 3 (NAMRU-3), Cairo, Egypt, after a maximum storage period of 5 days. Acute stool specimens from subjects with diarrhea were cultured immediately after collection in a laboratory established on the ship. Standard bacteriological methods were used to culture *Salmonella* ssp., *Shigella* ssp., *Yersinia enterocolitica*, *Campylobacter* ssp., *Vibrio* ssp., *Aeromonas hydrophila* group, and *Plesiomonas shigelloides*.

When present on the initial culture, 5 colonies of *E. coli* were selected and frozen at −20°C. Each was assayed for heat labile (LT) and heat stable (ST) enterotoxin using commercially available DNA probes (DuPont, Wilmington, DE). Enteroadherent *E. coli* strains (EAEC) were identified by adherence to HEp-2 cells in the presence of D-mannose.[13] Slide agglutination (Bio-Merieux, France) was used to identify enteropathogenic *E. coli* strains (EPEC) and all colonies that were sorbitol negative on Sorbitol-MacConkey agar were serotyped with O:157 antiserum to screen for enterohemorrhagic *E. coli* (EHEC) (DIFCO Labs, Detroit, MI). All *E. coli* that were initially lysine decarboxylase negative and nonmotile were further investigated for enteroinvasiveness by the Sereny test.[14]

The presence of protozoa and helminthic parasites was assessed by direct microscopic examination of fresh stool and specimens prepared by merthiolate-iodine-formalin concentration (MIFC). Methanol-fixed smears were stained with a modified acid fast stain and examined for *Cryptosporidium* oocysts. Stools were also examined for rotavirus by an enzyme-linked immunosorbent assay (Rotazyme, Abbott Laboratories).

Statistical analysis was performed using SPSS PC+ statistical package (SPSS Inc., Chicago, IL). The chi-square test with Yates correction was used for proportions; the Student's *t*-test was used for comparison of means. Mean values were reported as ± 1 SD. Efficacy of the drug was calculated as follows: [(percent ill in placebo group − percent ill in drug group)/percent ill in placebo group] × 100.[5]

RESULTS

Initially, 262 volunteers were enrolled in the study. Of these, 20 did not return for medication, 15 withdrew prior to reaching Alexandria or took no pills, 2 transferred from the ship, 2 did not respond to attempts at follow-up, and 1 went on emergency leave, making a total of 40 volunteers who did not complete the study. A total of 222 remained for analysis.

Pre-treatment stools were submitted by 129 of the subjects completing the study. The number of these pre-treatment stools positive for enteric pathogens in the placebo and norfloxacin groups were not statistically different (3/69 vs. 4/60, respectively). Pre-Alexandria positive cultures included 5 enterotoxigenic *E. coli* (ETEC) (3-LT+, 2-LT+ ST+) and 2 EAEC. None of the subjects with positive pre-treatment stools developed diarrhea.

As noted in Tables 1 and 2, there were no differences between the placebo and norfloxacin groups in terms of age, days ashore, number of meals, or types of foods eaten. Most subjects enrolled in the study made an organized excursion to Cairo as well as day trips to Alexandria.

The frequency of compliance and side effects did not differ between the groups. Subjects in the norfloxacin and placebo groups reported missing a mean of 0.5 ± 1.1 and 0.2 ± 0.8 doses, respectively ($P = 0.07$). Side effects were reported in 2.7% of the placebo group and 4% of the norfloxacin group ($P = 0.9$). There were 2 reports

of headache and 1 report each of dizziness, urinary symptoms, constipation, nausea, and localized rash. None of these were clinically significant or required discontinuation of the medication.

Norfloxacin gave significant protection against the development of acute diarrhea. Diarrhea developed in 25.6% (30/117) of the placebo group vs. 1.9% (2/105) of the norfloxacin group (93% protective efficacy). Compliance was a problem for the 2 study subjects in the norfloxacin group who developed diarrhea. One reported a single day of diarrhea after missing a dose of medication. He did not report for follow-up at the time of his illness, but submitted a normal stool 8 days after the diarrheal episode from which no enteric pathogen was isolated. The other subject reported missing medication for 2 days prior to developing diarrhea; this subject submitted no stool specimen.

Of the 32 who developed diarrhea, 1 norfloxacin and 17 placebo subjects submitted acute stool samples. Nine of these were positive for an enteric pathogen (Table 3). The majority of isolates were either enterotoxigenic *E. coli* or *Campylobacter*. A single stool contained both *Campylobacter* and rotavirus. All of the bacterial isolates were sensitive to norfloxacin.

TABLE 2

Comparison of exposure to diarrhea risk factors between norfloxacin and placebo groups

Factor (mean ± SD)	Placebo (n = 117*)	Norfloxacin (n = 105)	P value
Meals ashore	2.8 ± 2	2.8 ± 2	0.89
Hotel meals	1.3 ± 1.4	1.2 ± 1.1	0.43
Restaurant meals	1.2 ± 1.2	1.1 ± 1.5	0.9
Street vendor meals	0.1 ± 0.5	0.1 ± 0.4	0.9
History of consuming (no. yes/total)*			
Tap water	9/117	6/105	0.75
Bottled water	86/117	72/105	0.51
Ice	31/117	30/105	0.85
Salad	26/117	28/105	0.54
Dairy products	43/116	34/104	0.59
Meat	91/117	81/105	0.97
Seafood	15/115	15/104	0.92
Dessert	52/116	50/105	0.78
Fruit	22/117	22/104	0.79
Buffet meals	60/117	53/104	0.98

* Totals differ with no. of questionnaire responses.

DISCUSSION

Norfloxacin was effective for the short term prophylaxis of acute diarrhea in U.S. Naval and Marine Corps personnel on shore leave in Egypt. Comparable demographic and epidemiologic data between the treatment and control groups indicate that both groups were at a similar risk of infection. The failures occurred in subjects who did not comply with the study regimen.

This study confirms findings in Mexico that norfloxacin is effective taken once daily as compared to the twice daily regimen used in Swedish travelers.[10,11] It also supports norfloxacin's efficacy among different study populations and in different areas of the world.

There were no serious clinical side effects. This may in part be due to the short duration of the study, although norfloxacin has been generally well tolerated even when given for up to 6 weeks for treatment of urinary tract infections.[7] In 2 longer prophylaxis trials with norfloxacin, side effects were minimal.[10,11]

The antimicrobial agents doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) have undergone extensive evaluation as diarrhea prophylactic agents. Doxycycline is effective in areas where most of the isolates are sensitive, but the efficacy decreases in areas where enterotoxigenic *E. coli* are resistant.[9] Doxycycline resistant *E. coli* strains develop during therapy.[4] In addition, a recent study of U.S. Army personnel in Thailand who were taking doxycycline for malaria prophylaxis identified doxycycline-resistant *Campylobacter* as the etiologic agent in 50% of the diarrhea cases.[15]

Resistance to norfloxacin does not develop as rapidly as with nalidixic acid. Point mutations leading to increased MICs occur at a very low frequency, and although serial passage in the presence of the drug has lead to high-level resistance, norfloxacin inhibits the transfer of plasmids that may mediate resistance.[16,17] However, an isolate of *Shigella dysenteriae* with plasmid mediated resistance to nalidixic acid has been reported.[18] During a previous prophylaxis trial with norfloxacin, resistant bacteria were not observed.[11]

Antibiotic prophylaxis in this study was effective, but the question of whether to use antibiotics for prevention remains controversial.[19] Dietary measures are the simplest and safest methods of prevention, but it has been difficult

TABLE 3

Etiologic agents identified in acute stool specimens of subjects with diarrhea

Organism identified	Study group: Placebo (n = 30)	Study group: Norfloxacin (n = 2)
ETEC	5	0
Campylobacter	2	0
EAEC	1	0
Rotavirus	1	0
Entamoeba histolytica	1	0
None	8	0
No stool submitted	13	1

to show that these measures are effective. The benefits of prophylaxis must be weighed against the potential side effects for the individual and against the global concern of emerging resistant organisms. Consequently, antibiotic prophylaxis may be appropriate only for selected populations who have a special reason to avoid developing acute diarrhea. Norfloxacin may have some advantages in terms of the spectrum of antibacterial activity, infrequent side effects, and a lower potential for development of resistant bacteria. Most individuals, however, have a rapid response to therapy when treated soon after symptoms develop, and do not require prophylaxis.

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